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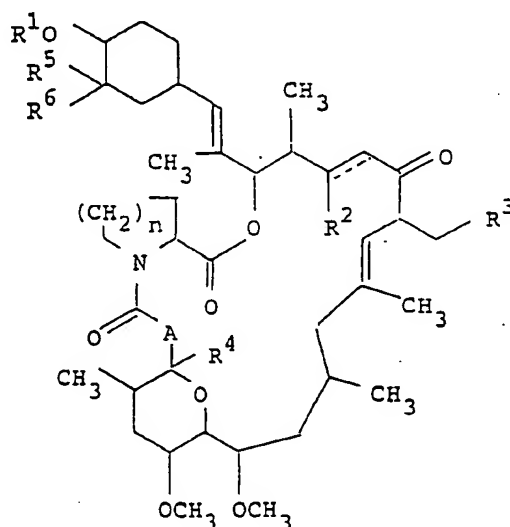
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(54) Title: TRICYCLO COMPOUNDS, A PROCESS FOR THEIR PRODUCTION AND A PHARMACEUTICAL COMPOSITION CONTAINING THE SAME



(I)

(57) Abstract

Compounds of formula (I) are disclosed, wherein R¹ is hydrogen or acyl, R² is hydrogen, hydroxy, alkoxy or acyloxy, R³ is (C₃-C₇)alkyl, aryl(C₂-C₇)alkyl, protected carboxy(C₂-C₇)alkyl, 1-(C₂-C₇)alkenyl, aryl-1-(C₂-C₇)alkenyl or protected carboxy-1-(C₂-C₇)alkenyl, R⁴ is hydroxy or alkoxy, R⁵ is hydrogen and R⁶ is hydroxy or methoxy, or R⁵ and R⁶ are combined to form oxo, A is methylene, hydroxymethylene or carbonyl, n is an integer of 1 or 2, and the symbol of a line and dotted line is a single bond or a double bond and salts thereof. And processes for their production, and pharmaceutical compositions containing them are also described.

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DESCRIPTIONTRICYCLO COMPOUNDS, A PROCESS FOR THEIR PRODUCTION AND
A PHARMACEUTICAL COMPOSITION CONTAINING THE SAME

5

This invention relates to novel tricyclo compounds having pharmacological activities, to a process for their production and to a pharmaceutical composition containing the same.

10

More particularly, it relates to novel tricyclo compounds, which have pharmacological activities such as immunosuppressive activity, antimicrobial activity, and the like, to a process for their production, to a pharmaceutical composition containing the same and to a use thereof as a medicament.

15

Accordingly, one object of this invention is to provide the novel tricyclo compounds, which are useful for treatment and prevention of resistance by transplantation, graft-versus-host diseases by medulla ossium transplantation, autoimmune diseases, infectious diseases, and the like.

20

Another object of this invention is to provide a process for production of the tricyclo compounds by synthetic process.

25

A further object of this invention is to provide a pharmaceutical composition containing, as active ingredients, the tricyclo compounds.

30

Still further object of this invention is to provide a use of the tricyclo compounds as a medicament for

treating and preventing resistance by transplantation,
graft-versus-host diseases by medulla ossium
transplantation, autoimmune diseases, infectious diseases,
and the like.

5

European Patent Application 184162 (Fujisawa
Pharmaceutical Co. Ltd.) discloses a number of macrocyclic
compounds isolated from microorganisms belonging to genus
10 Streptomyces such as Streptomyces tsukubaensis No. 9993
(FERM BP-927) and Streptomyces hygroscopicus subsp.
yakushimaensis No. 7238 (FERM BP-928). Such macrolides
are particularly numbered FR-900506, FR-900520,
FR-900523 and FR-900525. And the preparation of some their
derivatives is also described.

15

International Patent Application WO 89/05304,
European Patent Application Nos. 353678, 349049, 349061,
356399, 402931, etc also disclose a number of macrocyclic
immunosuppressive compounds.

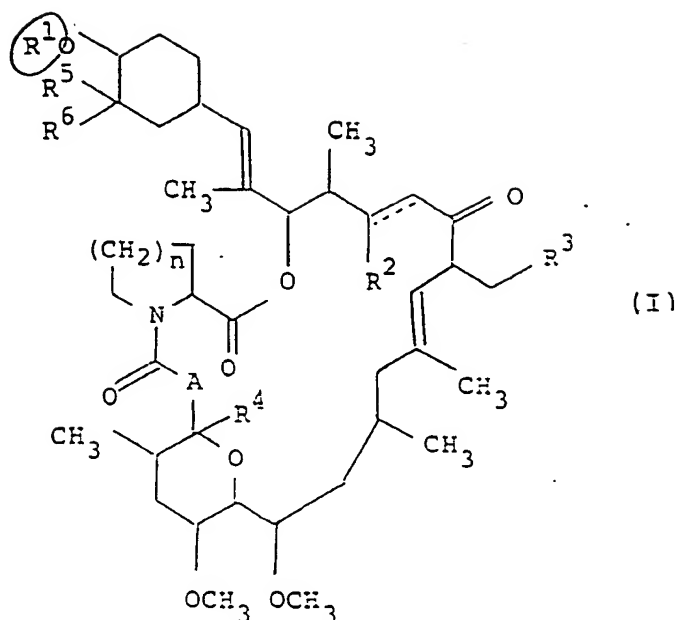
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We have now found a novel group of compounds which
possess certain advantageous properties over those
disclosed previously.

25

Thus, according to the invention, we provide a new
compound of the following formula:

(continued on the next page)



wherein R^1 is hydrogen or acyl,

R^2 is hydrogen, hydroxy, alkoxy or acyloxy,

15 R^3 is (C_3-C_7) alkyl, aryl (C_2-C_7) alkyl, protected carboxy (C_2-C_7) alkyl, 1- (C_3-C_7) alkenyl, aryl-1- (C_2-C_7) alkenyl or protected carboxy-1- (C_2-C_7) alkenyl,

R^4 is hydroxy or alkoxy,

20 R^5 is hydrogen and R^6 is hydroxy or methoxy, or R^5 and R^6 are combined to form oxo,

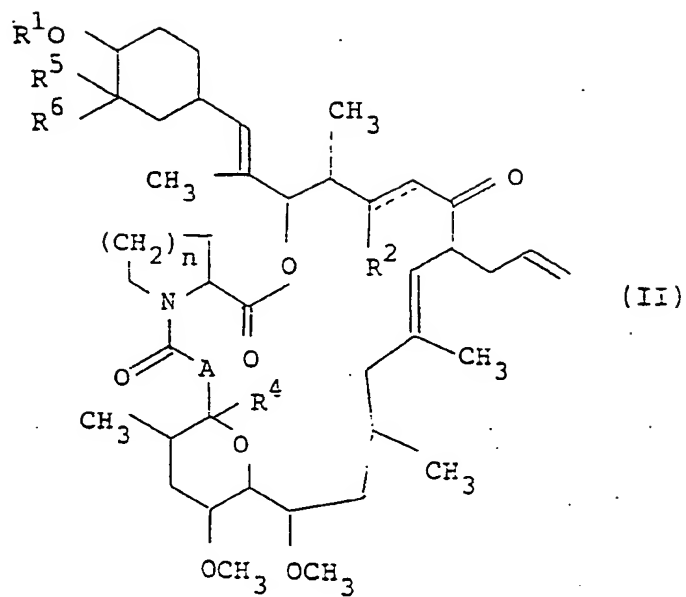
A is methylene, hydroxymethylene or carbonyl,

n is an integer of 1 or 2, and

25 the symbol of a line and dotted line is a single bond or a double bond.

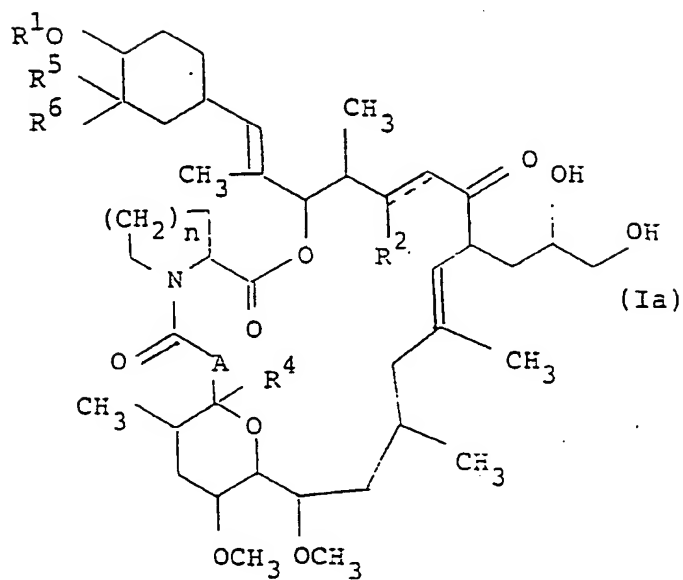
With respect to the tricyclo compounds (I) of this invention, it is to be understood that there may be one or more conformer(s) or stereoisomeric pairs such as optical and geometrical isomers due to asymmetric carbon atom(s) and double bond(s), and such isomers are also included within a scope of this invention.

35 According to this invention, the object tricyclo compounds (I) can be prepared by the following processes.

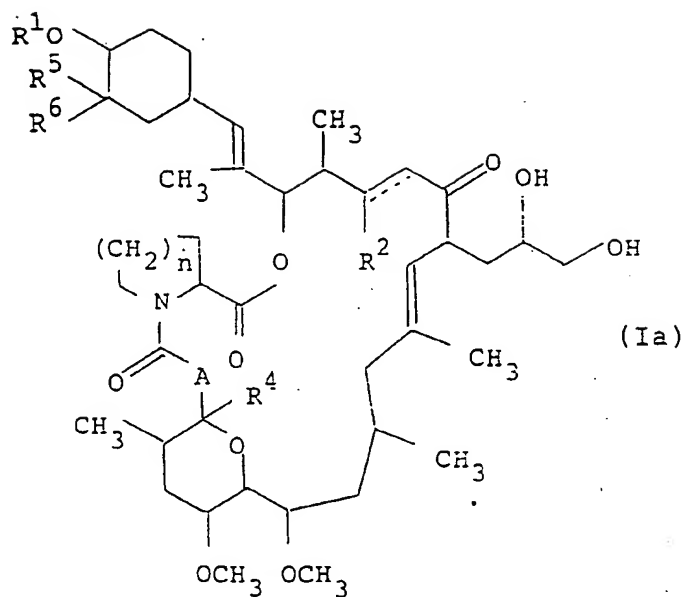
Process 1

or a salt thereof

Hydroxylation

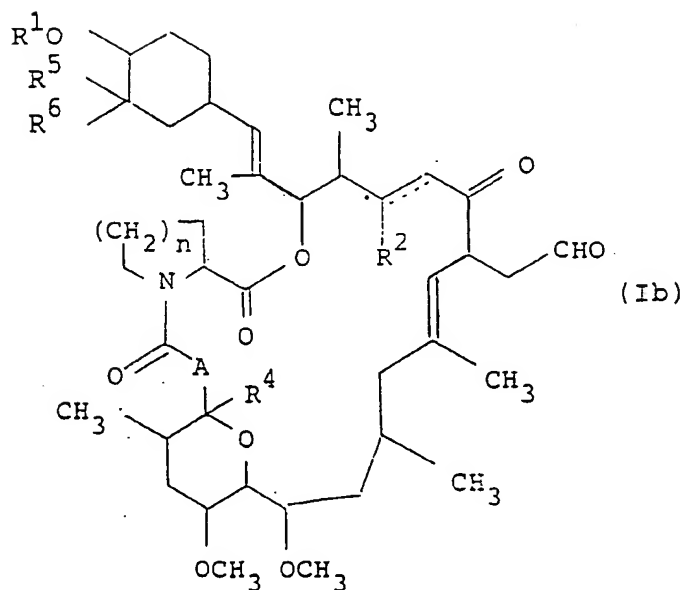


or a salt thereof

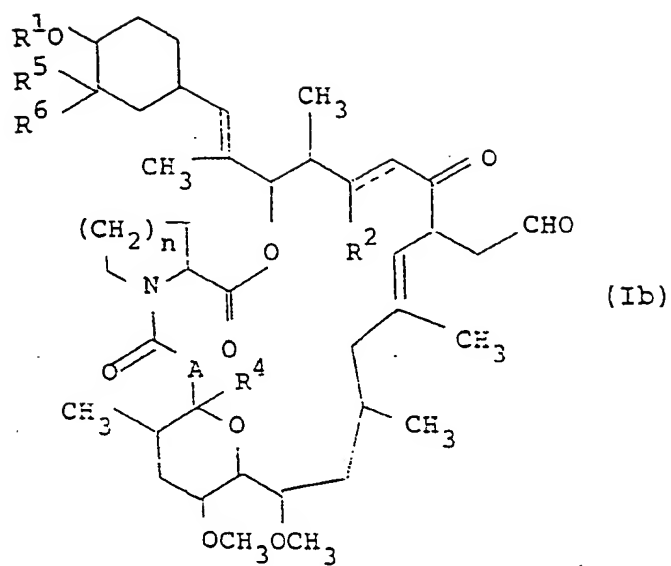
Process 2

or a salt thereof

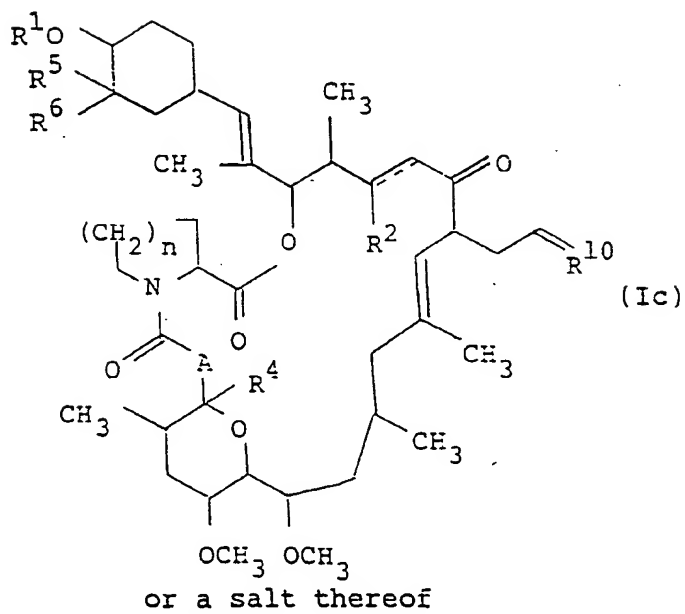
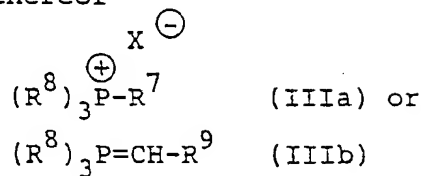
Oxidation



or a salt thereof

Process 3

or a salt thereof

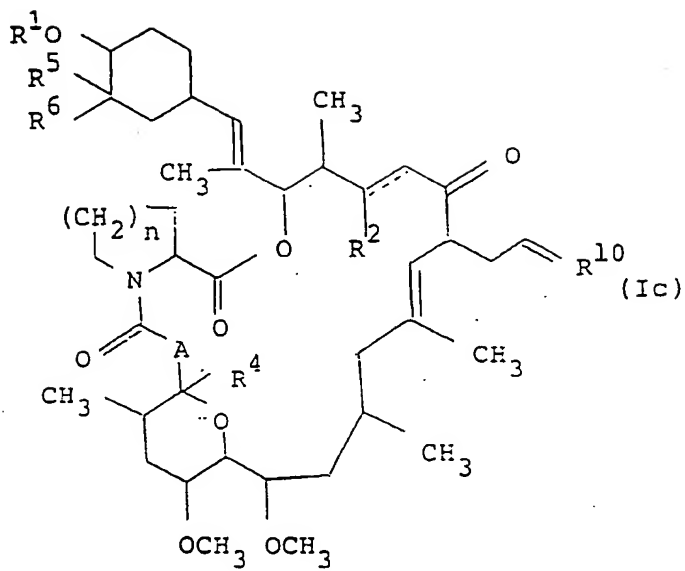


Process 4

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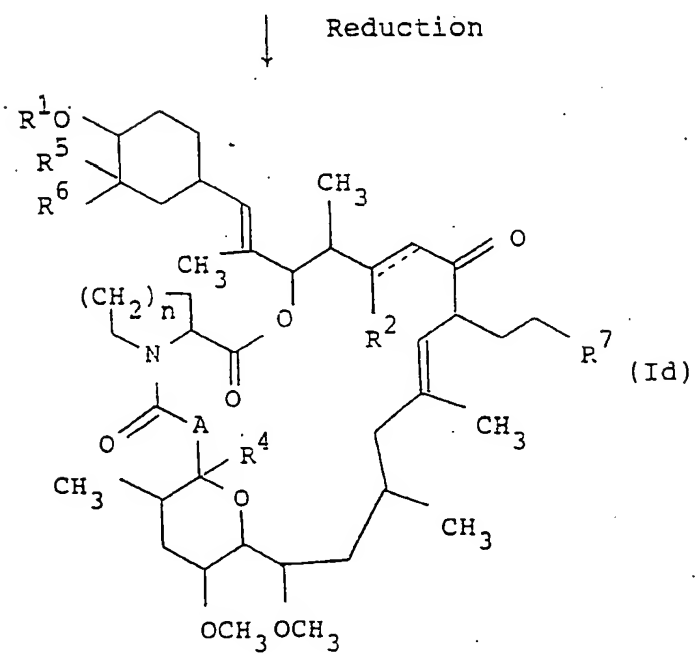
or a salt thereof

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25

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35



or a salt thereof

in which R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , A and n are each as defined above,

R^7 is (C_2-C_6) alkyl, aryl(C_1-C_6)alkyl or protected carboxy(C_1-C_6)alkyl,

5 R^8 is aryl,

R^9 is protected carboxy,

R^{10} is (C_2-C_6) alkylidene, aryl(C_1-C_6)alkylidene or protected carboxy(C_1-C_6)alkylidene, and

X is halogen.

10

Particulars of the above definitions and the preferred embodiments thereof are explained in detail as follows.

15 The term "lower" used in the specification is intended to mean 1 to 6 carbon atoms, unless otherwise indicated.

Suitable "acyl" and acyl group in the "acyloxy" may include aliphatic acyl, aromatic acyl and aliphatic acyl substituted with aromatic group, which are derived from 20 carboxylic, sulfonic and carbamic acids; and the like.

The aliphatic acyl may include lower alkanoyl which may have one or more suitable substituent(s) such as 25 carboxy (e.g. formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, carboxyacetyl, carboxypropionyl, carboxybutyryl, carboxyhexanoyl, etc.), cyclo(lower)alkyloxy(lower)-alkanoyl which may have one or more suitable 30 substituent(s) such as lower alkyl (e.g. cyclopropyloxyacetyl, cyclobutyloxypropionyl, cycloheptyloxybutyryl, menthyloxyacetyl, menthyloxypropionyl, menthyloxybutyryl, menthyloxyheptanoyl, menthyloxyhexanoyl, etc.), 35 camphorsulfonyl, lower alkylcarbamoyl having one or more

suitable substituent(s) such as carboxy, protected carboxy and hydroxy for example, carboxy(lower)alkylcarbamoyle (e.g. carboxymethylcarbamoyle, carboxyethylcarbamoyle, carboxypropylcarbamoyle, carboxybutylcarbamoyle, carboxypentylcarbamoyle, carboxyhexylcarbamoyle, etc.),
5 protected carboxy(lower)alkylcarbamoyle such as tri(lower)-
alkylsilyl(lower)alkoxycarbonyl(lower)alkylcarbamoyle (e.g. trimethylsilylmethoxycarbonylethylcarbamoyle, trimethylsilylethoxycarbonylpropylcarbamoyle,
10 triethylsilylethoxycarbonylpropylcarbamoyle, tert-butyl dimethylsilylethoxycarbonylpropylcarbamoyle, trimethylsilylpropoxycarbonylbutylcarbamoyle, etc.), hydroxy(lower)alkylcarbamoyle (e.g. hydroxymethylcarbamoyle, hydroxyethylcarbamoyle, hydroxypropylcarbamoyle,
15 hydroxybutylcarbamoyle, ~~hydroxypentylcarbamoyle~~,
~~hydroxyhexylcarbamoyle, etc.), and the like.~~

The aromatic acyl may include aroyl which may have one or more suitable substituent(s) such as nitro (e.g.
20 benzoyl, toluoyl, xyloyl, naphthoyl, nitrobenzoyl, dinitrobenzoyl, nitronaphthoyl, etc.), arenesulfonyl which may have one or more suitable substituent(s) such as halogen (e.g. benzenesulfonyl, toluenesulfonyl, xylenesulfonyl, naphthalenesulfonyl,
25 fluorobenzenesulfonyl, chlorobenzenesulfonyl, bromobenzenesulfonyl, iodobenzenesulfonyl, etc.), arylcarbamoyle which may have one or more suitable substituent(s) such as halogen (e.g. phenylcarbamoyle, fluorophenylcarbamoyle, chlorophenylcarbamoyle, etc.), and
30 the like.

The heterocyclic acyl may include heterocyclic carbonyl (e.g. furoyl, thenoyl, nicotinoyl, isonicotinoyl, thiazolylcarbonyl, thiadiazolylcarbonyl,
35 tetrazolylcarbonyl, morpholinocarbonyl, etc.), and the like.

The aliphatic acyl substituted with aromatic group may include ar(lower)alkanoyl which may have one or more suitable substituent(s) such as lower alkoxy and trihalo(lower)alkyl (e.g. phenylacetyl, phenylpropionyl, phenylbutyryl, 2-trifluoromethyl-2-methoxy-2-phenylacetyl, 2-ethyl-2-trifluoromethyl-2-phenylacetyl, 2-trifluoromethyl-2-propoxy-2-phenylacetyl, etc.), and the like.

The more preferred acyl group thus defined may be C_1-C_4 alkanoyl which may have carboxy, cyclo(C_5-C_6)-alkyloxy(C_1-C_4)alkanoyl having two (C_1-C_4)alkyl groups on the cycloalkyl moiety, camphorsulfonyl, carboxy(C_1-C_4)-alkylcarbamoyl, hydroxy(C_1-C_4)alkylcarbamoyl, tri(C_1-C_4)alkylsilyl(C_1-C_4)alkoxycarbonyl(C_1-C_4)alkylcarbamoyl, haloarylcarbamoyl, benzoyl which may have one or two nitro, benzenesulfonyl having halogen, phenyl(C_1-C_4)alkanoyl having C_1-C_4 alkoxy and trihalo(C_1-C_4)alkyl, morpholinocarbonyl, and the most preferred one may be acetyl, carboxypropionyl, menthyloxyacetyl, camphorsulfonyl, hydroxypropylcarbamoyl, benzoyl, nitrobenzoyl, dinitrobenzoyl, iodobenzenesulfonyl, phenylcarbamoyl, fluorophenylcarbamoyl, chlorophenylcarbamoyl, 2-trifluoromethyl-2-methoxy-2-phenylacetyl and morpholinocarbonyl.

Suitable alkoxy may be lower alkoxy such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, pentoxy, isopentoxy, neopentoxy, hexyloxy and the like, in which the preferred one is C_1-C_4 alkoxy.

Suitable " (C_3-C_7) alkyl" may include straight or branched one such as propyl, isopropyl, butyl, isobutyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, and the like, in which more preferred example may be (C_3-C_5) alkyl and

the most preferred one may be propyl and pentyl.

5 Suitable "(C₂-C₆)alkyl" may include straight or branched one such as ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, isopentyl, neopentyl, hexyl, and the like, in which more preferred example may be (C₂-C₄)alkyl and the most preferred one may be ethyl and butyl.

10 Suitable "aryl(C₂-C₇)alkyl" may include aforementioned (C₃-C₇)alkyl and ethyl, which are substituted with aryl, as mentioned below, wherein more preferred example may be phenyl(C₂-C₄)alkyl and the most preferred one may be 2-phenylethyl.

15 Suitable "protected carboxy(C₂-C₇)alkyl" may include aforementioned (C₃-C₇)alkyl and ethyl, which is substituted with protected carboxy as mentioned below, wherein more preferred example may be (C₁-C₄)alkoxycarbonyl(C₂-C₄)alkyl and the most preferred
20 one may be 2-methoxycarbonylethyl.

25 Suitable "1-(C₃-C₇)alkenyl" may include straight or branched one such as 1-propenyl, 1-isopropenyl, 1-butenyl, 1-isobutenyl, 1-pentenyl, 1-isopentenyl, 1-neopentenyl, 1-hexenyl, 1-heptenyl, and the like, in which more preferred example may be 1-(C₃-C₅)alkenyl and the most preferred one may be 1-propenyl and 1-pentenyl.

30 Suitable "aryl-1-(C₂-C₇)alkenyl" may include aforementioned 1-(C₃-C₇)alkenyl and ethenyl, which are substituted with aryl as mentioned below, wherein more preferred example may be phenyl-1-(C₂-C₄)alkenyl and the most preferred one may be 2-phenylethenyl.

35 Suitable "protected carboxy-1-(C₂-C₇)alkenyl" may include aforementioned 1-(C₃-C₇)alkenyl and ethenyl, which

is substituted with protected carboxy as mentioned below,
wherein more preferred example may be

(C₁-C₄)alkoxycarbonyl-1-(C₂-C₄)alkenyl and the most
preferred one may be 2-methoxycarbonylethenyl.

5

Suitable "aryl(C₁-C₆)alkyl" may include straight or
branched one such as methyl, ethyl, propyl, isopropyl,
butyl, isobutyl, pentyl, isopentyl, neopentyl, hexyl, and
the like, which is substituted with aryl as mentioned
below, wherein more preferred example may be
phenyl(C₁-C₄)alkyl and the most preferred one may be
benzyl.

10

Suitable "protected carboxy(C₁-C₆)alkyl" may include
straight or branched one such as methyl, ethyl, propyl,
isopropyl, butyl, isobutyl, pentyl, isopentyl, neopentyl,
hexyl, and the like, which is substituted with protected
carboxy as mentioned below, wherein more preferred example
may be (C₁-C₄)alkoxycarbonyl(C₁-C₄)alkyl.

15

20

Suitable "(C₂-C₆)alkylidene" may include straight or
branched one such as ethylidene, propylidene,
isopropylidene, butylidene, pentylidene, hexylidene, and
the like in which more preferred example may be
(C₂-C₄)alkylidene and the most preferred one may be
ethylidene and butylidene.

25

Suitable "aryl(C₁-C₆)alkylidene" may include
aforementioned (C₂-C₆)alkylidene and methylene, which are
substituted with aryl as mentioned below, wherein more
preferred example may be phenyl(C₁-C₄)alkylidene and the
most preferred one may be benzylidene.

30

Suitable "protected carboxy(C₁-C₆)alkylidene" may
include aforementioned (C₂-C₆)alkylidene and methylene,
which are substituted with protected carboxy as mentioned
below, wherein more preferred example may be

35

(C₁-C₄)alkoxycarbonyl(C₁-C₄)alkylidene and the most preferred one may be methoxycarbonylmethylene.

5 Suitable "leaving group" may include an acid residue and the like, and suitable examples of "acid residue" may be halogen (e.g. chlorine, bromine, iodine, etc.), sulfonyloxy (e.g. methanesulfonyloxy, benzenesulfonyloxy, toluenesulfonyloxy, etc.) or the like.

10 Suitable "protected carboxy" may include esterified carboxy such as lower alkoxycarbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, tert-butoxycarbonyl, etc.), mono(or di or tri)phenyl(lower)alkoxycarbonyl which
15 may have a nitro group (e.g. benzyloxycarbonyl, 4-nitrobenzyloxycarbonyl, phenethyloxycarbonyl, benzhydryloxycarbonyl, trityloxycarbonyl, etc.), and the like, in which more preferred example may be C₁-C₄ alkoxycarbonyl and the most preferred one may be
20 methoxycarbonyl.

25 Suitable "aryl" may include phenyl, tolyl, xylyl, cumenyl, mesityl, naphthyl, and the like, in which the preferred example may be phenyl.

30 Suitable "halogen" may be chlorine bromine, fluorine and iodine, in which the preferred one may be chlorine and bromine.

35 The processes for production of tricyclo compounds (I) of this invention are explained in detail in the following.

Process 1 :

35 The compound (Ia) or a salt thereof can be prepared

by hydroxylating the compound (II) or a salt thereof.

The hydroxylating agent applicable to this process may be a conventional one which is capable of introducing hydroxy group(s) into the allyl moiety of starting compound (II), for example, alkali metal permanganate (e.g. potassium permanganate, etc.), osmium tetroxide optionally in the presence of a suitable oxidizing agent to regenerate osmium tetroxide (e.g. N-methylmorpholine N-oxide, sodium chlorate, etc.), hydrogen peroxide, and the like.

This reaction is usually conducted in a conventional solvent which does not adversely influence the reaction such as water, methanol, ethanol, propanol, pyridine, ethyl acetate, N,N-dimethylformamide, dichloromethane, ethyl ether, isopropyl ether, 1,4-dioxane or a mixture thereof.

The reaction temperature of this reaction is not critical and the reaction is usually conducted under from cooling to warming.

Process 2 :

The compound (Ib) or a salt thereof can be prepared by oxidizing the compound (Ia) or a salt thereof to an aldehyde.

The oxidizing agent applicable to this process may be a conventional one which is capable of oxidizing vicinal diols to an aldehyde, for example, perhalogenic acid or a salt thereof (e.g. periodic acid, sodium metaperiodate, etc.), lead tetra(lower alkanoate) (e.g. lead tetraacetate, etc.), and the like.

This reaction is usually conducted in a conventional solvent which does not adversely influence the reaction such as water, methanol, ethanol, propanol, pyridine, ethyl acetate, N,N-dimethylformamide, dichloromethane, ethyl ether, isopropyl ether, 1,4-dioxane, or a mixture thereof.

The reaction temperature is not critical and the reaction is usually conducted under from cooling to warming.

Process 3 :

The compound (Ic) or a salt thereof can be prepared by reacting the compound (Ib) or a salt thereof with the compound (IIIa) or (IIIb).

In case that the compound (IIIa) is used in this reaction, this reaction can preferably be carried out in the presence of an organic or inorganic base such as lower alkylalkalimetal (e.g. methylolithium, butyllithium, etc.), alkali metal (e.g. lithium, sodium, potassium, etc.), alkaline earth metal (e.g. calcium, etc.), alkali metal hydride (e.g. sodium hydride, etc.), alkaline earth metal hydride (e.g. calcium hydride, etc.), alkali metal hydroxide (e.g. sodium hydroxide, potassium hydroxide, etc.), alkali metal carbonate (e.g. sodium carbonate, potassium carbonate, etc.), alkali metal hydrogen carbonate (e.g. sodium hydrogen carbonate, potassium hydrogen carbonate, etc.), alkali metal alkoxide (e.g. sodium methoxide, sodium ethoxide, potassium tert-butoxide, etc.), alkali metal alkanoic acid (e.g. sodium acetate, etc.), trialkylamine (e.g. triethylamine, etc.), pyridine compound (e.g. pyridine, lutidine, picoline, 4-N,N-dimethylaminopyridine, etc.), quinoline, and the like.

The reaction is usually conducted in a conventional solvent which does not adversely influence the reaction such as acetone, dichloromethane, alcohol (e.g. methanol, ethanol, etc.), tetrahydrofuran, pyridine, benzene, N,N-dimethylformamide, hexane, ethyl ether, isopropyl ether, 1,4-dioxane, etc., or a mixture thereof.

The reaction temperature is not critical and the reaction is usually conducted under from cooling to warming.

Process 4 :

The compound (Id) or a salt thereof can be prepared by reducing the compound (Ic) or a salt thereof.

The reduction method applicable for this reaction is a conventional one which is capable of hydrogenating olefinic bond and may include, for example, reduction by using a combination of a metal (e.g. zinc, zinc amalgam, etc.) or a chrome compound (e.g. chromous chloride, chromous acetate, etc.) and an organic or inorganic acid (e.g. acetic acid, propionic acid, hydrochloric acid, sulfuric acid, etc.); and conventional catalytic reduction in the presence of a conventional metallic catalyst such as palladium catalysts (e.g. spongy palladium, palladium black, palladium oxide, palladium on carbon, colloidal palladium, palladium on barium sulfate, palladium on barium carbonate, palladium hydroxide on carbon, etc.), nickel catalysts (e.g. reduced nickel, nickel oxide, Raney nickel, etc.), platinum catalysts (e.g. platinum plate, spongy platinum, platinum black, colloidal platinum, platinum oxide, platinum wire, etc.); rhodium on alumina powder, sodium borohydride, a combination of tri(lower)alkylborane and sodium borohydride, diisobutylaluminum hydride, and the like.

This reaction is usually carried out in a conventional solvent which does not adversely influence the reaction such as water, alcohol (e.g. methanol, ethanol, propanol, etc.), dioxane, tetrahydrofuran, acetic acid, buffer solution (e.g. phosphate buffer, acetate buffer, etc.), benzene, toluene, xylene, and the like, or a mixture thereof.

The reaction temperature is not critical and the reaction is usually carried out under from cooling to warming.

The object tricyclo compounds (I) obtained according to the processes as explained above can be isolated and purified in a conventional manner, for example, extraction, precipitation, fractional crystallization, recrystallization, chromatography, and the like.

Suitable salts of the compounds (I), (Ia), (Ib), (Ic), (Id) and (II) may include pharmaceutically acceptable salts such as basic salts, for example, alkali metal salt (e.g. sodium salt, potassium salt, etc.), alkaline earth metal salt (e.g. calcium salt, magnesium salt, etc.), ammonium salt, amine salt (e.g. triethylamine salt, N-benzyl-N-methylamine salt, etc.) and other conventional organic salts.

With respect to the tricyclo compounds (II) of this invention, it is to be understood that there may be one or more conformer(s) or stereoisomeric pairs such as optical and geometrical isomers due to asymmetric carbon atom(s) and double bond(s), and such isomers are also included within a scope of this invention.

The starting compound (II) in the process mentioned above contains known and novel compounds, and the known

compounds are disclosed, for example, in European Patent Publication Nos. 184162 and 323042 and the new compound can be prepared by a conventional manner.

5 PHARMACOLOGICAL ACTIVITIES OF THE TRICYCLO COMPOUNDS

 The tricyclo compounds (I) possess pharmacological activities such as immunosuppressive activity, antimicrobial activity, and the like, and therefore are
10 useful for the treatment and prevention of immune-mediated diseases controlled by a immunosuppressant such as the resistance by transplantation of organs or tissue such as heart, kidney, liver, medulla ossium, skin, cornea, lung, pancreas, intestinum tenue, limb, muscle, nervus, etc.;
15 graft-versus-host diseases by medulla ossium transplantation; autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, Hashimoto's thyroiditis, multiple sclerosis, myasthenia gravis, type I diabetes, and the like; and further infectious diseases
20 caused by pathogenic microorganisms.

 Further, the tricyclo compounds (I) are also useful for the treatment and the prophylaxis of inflammatory and
25 hyperproliferative skin diseases and cutaneous manifestations of immunologically-mediated illnesses, such as, psoriasis, atopic dermatitis, contact dermatitis and further eczematous dermatitises, seborrhoeic dermatitis, Lichen planus, Pemphigus; bullous Pemphigoid, Epidermolysis
30 bullosa, urticaria, angioedemas, vasculitides, erythemas, cutaneous eosinophilias, Lupus erythematosus, acne and Alopecia areata;
 various eye diseases such as autoimmune diseases and so on (e.g. keratoconjunctivitis, vernal conjunctivitis, uveitis
35 associated with Behcet's disease, keratitis, herpetic keratitis, conical cornea, dystrophia epithelialis corneae,

corneal leukoma, ocular pemphigus, Mooren's ulcer, Scleritis, Graves' ophthalmopathy, etc.);

5 reversible obstructive airways disease, which includes conditions such as asthma (e.g. bronchial asthma, allergic asthma, intrinsic asthma, extrinsic asthma and dust asthma), particularly chronic or inveterate asthma (e.g. late asthma and airway hyper-responsiveness), bronchitis and the like;

10 inflammation of mucosa and blood vessels such as gastric ulcers, vascular damage caused by ischemic diseases and thrombosis, ischemic bowel disease, inflammatory bowel disease, necrotizing enterocolitis, intestinal lesions associated with thermal burns, leukotriene B₄-mediated diseases;

15 intestinal inflammations/allergies such as Coeliac disease, proctitis, eosinophilic gastroenteritis, mastocytosis, Crohn's disease and ulcerative colitis;

food related allergic diseases which have symptomatic manifestation remote from the gastro-intestinal tract, for

20 example migraine, rhinitis and eczema;

renal diseases selected from interstitial nephritis, Goodpasture's syndrome, hemolytic-uremic syndrome and diabetic nephropathy;

nervous diseases selected from multiple myositis,

25 Guillain-Barré syndrome, Ménière's disease and radiculopathy;

endocrine diseases selected from hyperthyroidism and Basedow's disease;

hematic diseases selected from pure red cell aplasia,

30 aplastic anemia, hypoplastic anemia, idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia, agranulocytosis and anerythroplasia;

bone diseases such as osteoporosis;

respiratory diseases selected from sarcoidosis, fibroid lung

35 and idiopathic interstitial pneumonia;

skin diseases selected from dermatomyositis, leukoderma
vulgaris, ichthyosis vulgaris, photoallergic sensitivity and
cutaneous T cell lymphoma;
circulatory diseases selected from arteriosclerosis,
5 atherosclerosis, aortitis syndrome, polyarteritis nodosa and
myocardosis;
collagen diseases selected from scleroderma, Wegener's
granuloma and Sjogren's syndrome;
adiposis;
10 eosinophilic fasciitis;
periodontal disease;
nephrotic syndrome such as glomerulonephritis;
hemolytic-uremic syndrome;
photoallergic sensitivity;
15 male pattern alopecia or alopecia senilis; and so on.

And further, the tricyclo compounds (I) have liver
regenerating activity and/or activities of stimulating
hypertrophy and hyperplasia of hepatocytes. Therefore, they
20 are useful for the treatment and prevention of hepatic
diseases such as immunogenic diseases (e.g. chronic
autoimmune liver diseases selected from the group consisting
of autoimmune hepatitis, primary biliary cirrhosis and
sclerosing cholangitis), partial liver resection, acute
25 liver necrosis (e.g. necrosis caused by toxins, viral
hepatitis, shock or anoxia), B-virus hepatitis, non-A/non-B
hepatitis and cirrhosis.

And further, the tricyclo compounds (I) are useful for
30 various diseases because of its useful pharmaceutical
activity such as augmenting activity of chemotherapeutic
effect.

As examples for showing such pharmacological
35 activities, the pharmacological test data of the tricyclo
compounds (I) is illustrated in the following.

Test 1Suppression of in vitro Mixed Lymphocyte Reaction (MLR)

The MLR test was performed in microtiter plates, with each well containing 5×10^5 C57BL/6 responder cells (H-2^b), 5×10^5 mitomycin C treated (25 μ g/ml mitomycin C at 37°C for 30 minutes and washed three times with RPMI 1640 medium) BALB/C stimulator cells (H-2^d) in 0.2 ml RPMI 1640 medium supplemented with 10% fetal calf serum, 2mM sodium bicarbonate, penicillin (50 unit/ml) and streptomycin (50 μ g/ml). The cells were incubated at 37°C in humidified atmosphere of 5% carbon dioxide and 95% of air for 68 hours and pulsed with ³H-thymidine (0.5 μ Ci) 4 hours before the cells were collected. The object compound of this invention were dissolved in ethanol and further diluted in RPMI 1640 medium and added to the cultures to give final concentrations of 100 nM or less.

The IC₅₀ value (mol concentration to suppress 50% of MLR) was calculated by a conventional method, which is shown in the following Table 1.

Table 1 : IC₅₀ Value of MLR test on tricyclo compounds (I)

Test compound	IC ₅₀ value (mol/liter)
tricyclo compound prepared in Example 9	4.1×10^{-9}

The pharmaceutical composition of this invention can be used in the form of a pharmaceutical preparation, for example, in solid, semisolid or liquid form, which contains the tricyclo compounds (I), as an active ingredient, in admixture with an organic or inorganic carrier or excipient suitable for external, enteral or

parenteral applications. The active ingredient may be compounded, for example, with the usual non-toxic, pharmaceutically acceptable carriers for tablets, pellets, capsules, suppositories, solutions, emulsions, suspensions, injections, ointments, liniments, eye drops lotion, gel, creme and any other form suitable for use. The carriers which can be used are water, glucose, lactose, gum acacia, gelatin, mannitol, starch paste, magnesium trisilicate, talc, corn starch, keratin, colloidal silica, potato starch, urea and other carriers suitable for use in manufacturing preparations, in solid, semisolid, or liquid form, and in addition auxiliary, stabilizing, thickening, solubilizing and coloring agents and perfumes may be used. Particularly, as a solubilizing agent, there may be exemplified water-soluble cellulose polymer (i.e. hydroxypropyl methylcellulose, etc.), water-soluble glycol (i.e. propylene glycol, etc.), etc. The active object compound is included in the pharmaceutical composition in an amount sufficient to produce the desired effect upon the process or condition of diseases.

For applying this composition to human, it is preferable to apply it by parenteral or enteral administration. While the dosage of therapeutically effective amount of the tricyclo compound (I) varies from and also depends upon the age and condition of each individual patient to be treated, a daily dose of about 0.01-1000 mg, preferably 0.1-500 mg and more preferably 0.5-100 mg, of the active ingredient is generally given for treating diseases, and an average single dose of about 0.5 mg, 1 mg, 5 mg, 10 mg, 50 mg, 100 mg, 250 mg and 500 mg is generally administered.

The following examples are given for the purpose of illustrating the present invention.

Example 1

A solution of 17-Allyl-1-hydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-
5 [22.3.1.0^{4,9}]octacos-18-ene-2,3,10,16-tetraone (2.57 g) in a mixture of 1,4-dioxane (40 ml) and water (4 ml) was treated with catalytic amount of osmium tetroxide in tetrahydrofuran and 4-methylmorpholine N-oxide (1.15 g), and stirring was continued for 5.5 hours at room
10 temperature. To this reaction mixture was added water, and the separated aqueous phase was extracted with diethyl ether. The combined organic layers were washed with water and brine, dried over magnesium sulfate and concentrated. The residue was purified by silica gel column
15 chromatography to give pure 1-hydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-17-(2,3-dihydroxypropyl)-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.0^{4,9}]octacos-18-ene-2,3,10,16-tetraone (1.91 g).
20 FAB MS : m/z 844 (M + Na)

Example 2

To a solution of 1-hydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-17-(2,3-dihydroxypropyl)-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.0^{4,9}]octacos-18-ene-2,3,10,16-tetraone (220 mg) in 1,4-dioxane (7 ml) was added a
25 solution of sodium metaperiodate (573 mg) in water (2 ml) at 0°C. After 1 hour at the same temperature, diethyl ether and water was added, and the separated aqueous phase was extracted with diethyl ether. The combined organic
30 layers were washed with brine, dried over magnesium sulfate, and concentrated in vacuo to give 17-formylmethyl-1-hydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-
35

azatricyclo[22.3.1.0^{4,9}]octacos-18-ene-2,3,10,16-tetraone (220 mg). This product was used to the next reaction without further purification.

¹H NMR (CDCl₃) : 9.70-9.78 (1H, m)

5

Example 3-1)

To a stirred suspension of n-butyltriphenylphosphonium bromide (505 mg) in diethyl ether (9.2 ml) at 0°C was added 1.4 M methyllithium in hexane (0.9 ml). The orange reaction mixture was warmed to room temperature and stirred for 2 hours. To a solution of 17-formylmethyl-1-hydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo- [22.3.1.0^{4,9}]octacos-18-ene-2,3,10,16-tetraone (150 mg) in diethyl ether (10 ml) was added the above obtained 0.13 M wittig reagent at 0°C and warmed to room temperature over 2 hours. The reaction mixture was washed with water and brine, and dried over magnesium sulfate. After evaporation, the residue was purified by silica gel column chromatography followed by chromatography on thin layer chromatography-grade silica gel to give 17-(2-hexenyl)-1-hydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.0^{4,9}]octacos-18-ene-2,3,10,16-tetraone (38 mg).

10

15

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25

FAB MS : m/z 852 (M + Na)

Example 3-2)

To a cold (0°C), magnetically stirred slurry of benzyltriphenylphosphonium chloride (650 mg) in diethyl ether (10 ml) was added dropwise methyllithium (1.2 ml of 1.4 M in tetrahydrofuran). This ylide solution was allowed to warm to room temperature. A solution of 17-formylmethyl-1-hydroxy-12-[2-(4-hydroxy-3-

30

35

methoxycyclohexyl)-1-methylvinyl]-23,25-dimethoxy-
13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-
[22.3.1.0^{4,9}]octacos-18-ene-2,3,10,16-tetraone (150 mg) in
diethyl ether (15 ml) was treated with recooled above
5 ylides solution (1.9 ml) at 0°C. The reaction mixture was
warmed to room temperature and stirred for one hour. The
mixture was quenched with water and diethyl ether was
added thereto. The organic layer was washed with water
and brine, dried over magnesium sulfate, and concentrated.
10 The residue was subjected to a chromatography on silica
gel (TLC grade) eluting with 70% ethyl acetate in n-hexane
to give 1-hydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-
methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-17-
(3-phenyl-2-propenyl)-11,28-dioxa-4-azatricyclo-
15 [22.3.1.0^{4,9}]octacos-18-ene-2,3,10,16-tetraone (70 mg).
FAB MS : m/z 886 (M + Na)

Example 4-1)

A solution of 17-(2-hexenyl)-1-hydroxy-12-[2-(4-
20 hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-23,25-
dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-
azatricyclo[22.3.1.0^{4,9}]octacos-18-ene-2,3,10,16-tetraone
(32 mg) in ethanol (2 ml) was admixed with Rhodium on
alumina powder (10 mg) and stirred for 3.3 hours under
25 atmospheric pressure of hydrogen. The catalyst was
separated by filtration through Celite. Concentration of
this filtrate gave 17-hexyl-1-hydroxy-12-[2-(4-hydroxy-
3-methoxycyclohexyl)-1-methylvinyl]-23,25-dimethoxy-
13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-
30 [22.3.1.0^{4,9}]octacos-18-ene-2,3,10,16-tetraone (25 mg).
FAB MS : m/z 827 (M + Na)

Example 4-2)

1-Hydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-
35 1-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-

17-[3-(phenyl)propyl]-11,28-dioxa-4-azatricyclo-
[22.3.1.0^{4,9}]octacos-18-ene-2,3,10,16-tetraone was
obtained in 57.6% yield in substantially the same manner
as that of Example 4-1).

5 FAB MS : m/z 888 (M + Na)

Example 5

17-(2-Butenyl)-1-hydroxy-12-[2-(4-hydroxy-3-methoxy-
cyclohexyl)-1-methylvinyl]-23,25-dimethoxy-13,19,21,27-
10 tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.0^{4,9}]octacos-
18-ene-2,3,10,16-tetraone was obtained in 22.5% yield in
substantially the same manner as those of Examples 2 and
3-1) by using butyllithium instead of methyllithium.

FAB MS : m/z 824 (M + Na)

15

Example 6

17-Butyl-1-hydroxy-12-[2-(4-hydroxy-3-methoxycyclo-
hexyl)-1-methylvinyl]-23,25-dimethoxy-13,19,21,27-
tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.0^{4,9}]octacos-
20 18-ene-2,3,10,16-tetraone was obtained in 80.8% yield in
substantially the same manner as that of Example 4-1).

FAB MS : m/z 827 (M + Na)

Example 7

25 A solution of 17-allyl-1,14-dihydroxy-12-[2-(4-
hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-23,25-
dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-
azatricyclo[22.3.1.0^{4,9}]octacos-18-ene-2,3,10,16-
tetraone (2.0 g) in tetrahydrofuran (30 ml) and water
30 (1 ml) was treated with catalytic amount of osmium
tetroxide in tetrahydrofuran and 4-methylmorpholine
N-oxide (873 mg) and stirring was continued for 2 hours at
room temperature. Then 4-methylmorpholine N-oxide (583
mg) was added and this mixture was stirred for additional
35 4 hours at the same temperature. To this reaction mixture

was added diethyl ether and water, and the separated aqueous phase was extracted with diethyl ether. The combined organic layer was washed in turn with water and brine, dried over magnesium sulfate and concentrated. The residue was purified by silica gel column chromatography (elution with ethyl acetate) to give pure 1,14-dihydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-17-(2,3-dihydroxypropyl)-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.0^{4,9}]octacos-18-ene-2,3,10,16-tetraone (1.4 g).

FAB MS : m/z 860 (M + Na)

Example 8

17-Formylmethyl-1,14-dihydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.0^{4,9}]octacos-18-ene-2,3,10,16-tetraone was obtained in quantitative yield in substantially the same manner as that of Example 2.

¹H NMR (CDCl₃, δ) : 9.70-9.78 (1H, m)

Example 9

17-(2-Butenyl)-1,14-dihydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.0^{4,9}]octacos-18-ene-2,3,10,16-tetraone was obtained in 2.4% yield in substantially the same manner as that of Example 3-1).

FAB MS : m/z 840 (M + Na)

Example 10-1)

1,14-Dihydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-17-(3-phenyl-2-propenyl)-11,28-dioxa-4-azatricyclo-[22.3.1.0^{4,9}]octacos-18-ene-2,3,10,16-tetraone was

obtained in 73.1% yield in substantially the same manner as those of Examples 2 and 3-2).

FAB MS : m/z 902 (M + Na)

5 Example 10-2)

To a solution of 1,14-dihydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-17-(2,3-dihydroxypropyl)-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.0^{4,9}]octacos-18-ene-2,3,10,16-tetraone (100 mg) in benzene (5 ml) was added lead tetraacetate (53 mg). The mixture was stirred at room temperature for 1 hour. Methyl (triphenylphosphoranylidene)acetate (120 mg) was added thereto and the stirring was continued for additional 16 hours.

10 Diethyl ether and water were added thereto and the organic layer was separated. The organic phase was washed with brine, dried over magnesium sulfate and concentrated. The residue was subjected to a silica gel column chromatography eluting with diethyl ether to give

20 1,14-dihydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-23,25-dimethoxy-17-(3-methoxycarbonyl-2-propenyl)-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.0^{4,9}]octacos-18-ene-2,3,10,16-tetraone (140 mg).

25 FAB MS : m/z 884 (M + Na).

Example 11-1)

1,14-Dihydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-17-[3-(phenyl)propyl]-11,28-dioxa-4-azatricyclo[22.3.1.0^{4,9}]-octacos-18-ene-2,3,10,16-tetraone was obtained in 40.2% yield in substantially the same manner as that of Example 4-1).

30

FAB MS : m/z 904 (M + Na)

35

Example 11-2)

A solution of 1,14-dihydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-23,25-dimethoxy-17-(3-methoxycarbonyl-2-propenyl)-13,19,21,27-tetramethyl-
5 11,28-dioxa-4-azatricyclo[22.3.1.0^{4,9}]octacos-18-one-2,3,10,16-tetraone (120 mg) in methanol (3 ml) was admixed with platinum oxide and stirred for one hour under atmospheric pressure of hydrogen. The catalyst was
10 separated by filtration through Celite. The filtrate was concentrated, and the residue was purified by thin layer chromatography to give 1,14-dihydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-23,25-dimethoxy-17-[3-(methoxycarbonyl)propyl]-13,19,21,27-tetramethyl-11,28-
15 dioxa-4-azatricyclo[22.3.1.0^{4,9}]octacos-18-ene-2,3,10,16-tetraone (10 mg).

FAB MS : m/z. 886 (M + Na)

20

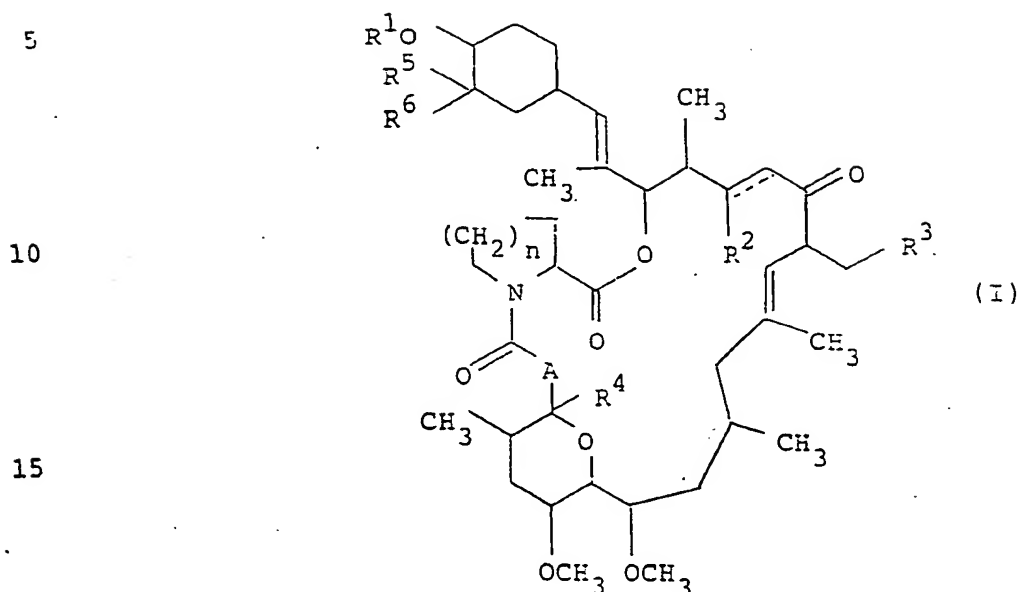
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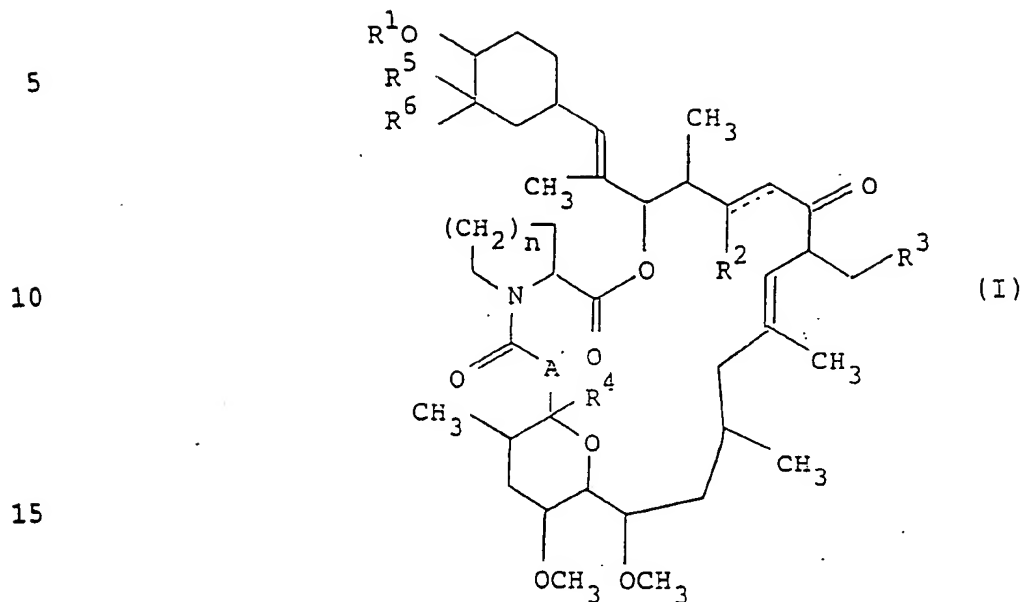
CLAIMS:

1. A compound of the formula :



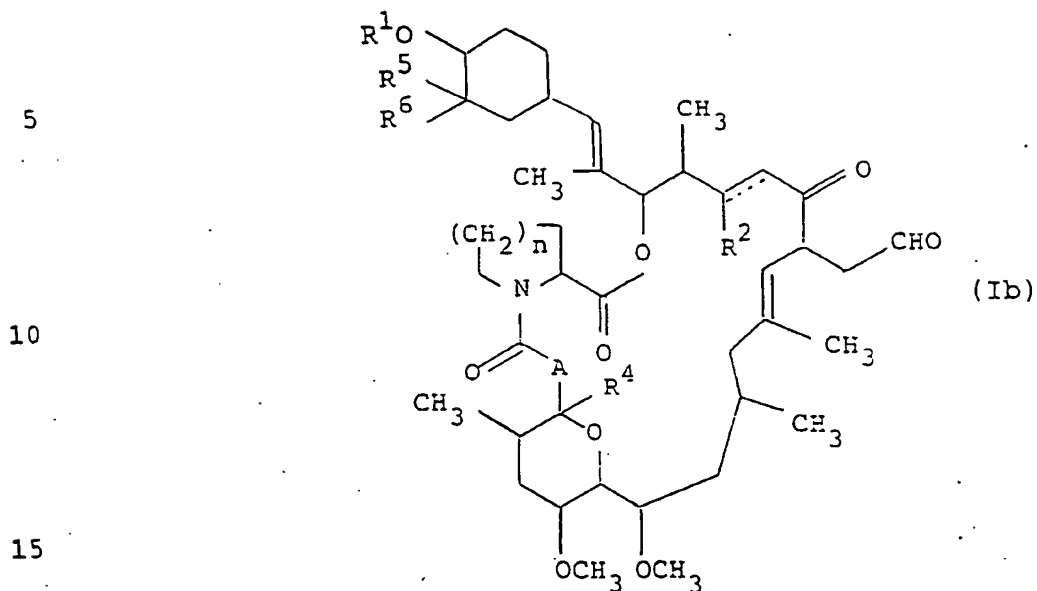
20 wherein R^1 is hydrogen or acyl,
 R^2 is hydrogen, hydroxy, alkoxy or acyloxy,
 R^3 is (C_3-C_7) alkyl, aryl (C_2-C_7) alkyl,
 protected carboxy (C_2-C_7) alkyl,
 1- (C_3-C_7) alkenyl, aryl-1- (C_2-C_7) alkenyl
 25 or protected carboxy-1- (C_2-C_7) alkenyl,
 R^4 is hydroxy or alkoxy,
 R^5 is hydrogen and R^6 is hydroxy or methoxy,
 or
 R^5 and R^6 are combined to form oxo,
 30 A is methylene, hydroxymethylene or
 carbonyl,
 n is an integer of 1 or 2, and
 the symbol of a line and dotted line is a
 single bond or a double bond,
 35 or a pharmaceutically acceptable salt thereof.

2. A process for the preparation of a compound of the formula :

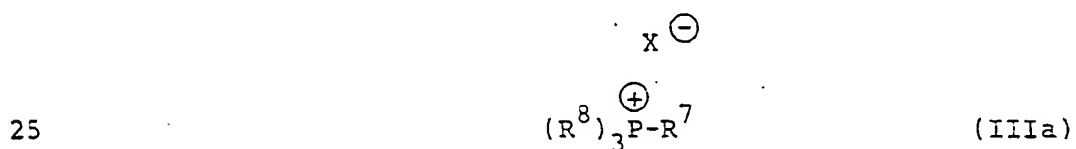


20 wherein R¹ is hydrogen or acyl,
R² is hydrogen, hydroxy, alkoxy or acyloxy,
R³ is (C₃-C₇)alkyl, aryl(C₂-C₇)alkyl,
protected carboxy(C₂-C₇)alkyl,
1-(C₃-C₇)alkenyl, aryl-1-(C₂-C₇)alkenyl
25 or protected carboxy-1-(C₂-C₇)alkenyl,
R⁴ is hydroxy or alkoxy,
R⁵ is hydrogen and R⁶ is hydroxy or methoxy,
or
R⁵ and R⁶ are combined to form oxo,
30 A is methylene, hydroxymethylene or
carbonyl,
n is an integer of 1 or 2, and
the symbol of a line and dotted line is a
single bond or a double bond,
35 or a salt thereof, which comprises

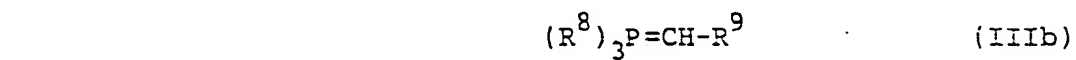
(a) reacting a compound of the formula :



wherein R^1 , R^2 , R^4 , R^5 , R^6 , A, n and the symbol of a
line and dotted line are each as
defined above,
or a salt thereof, with a compound of the formula :



or



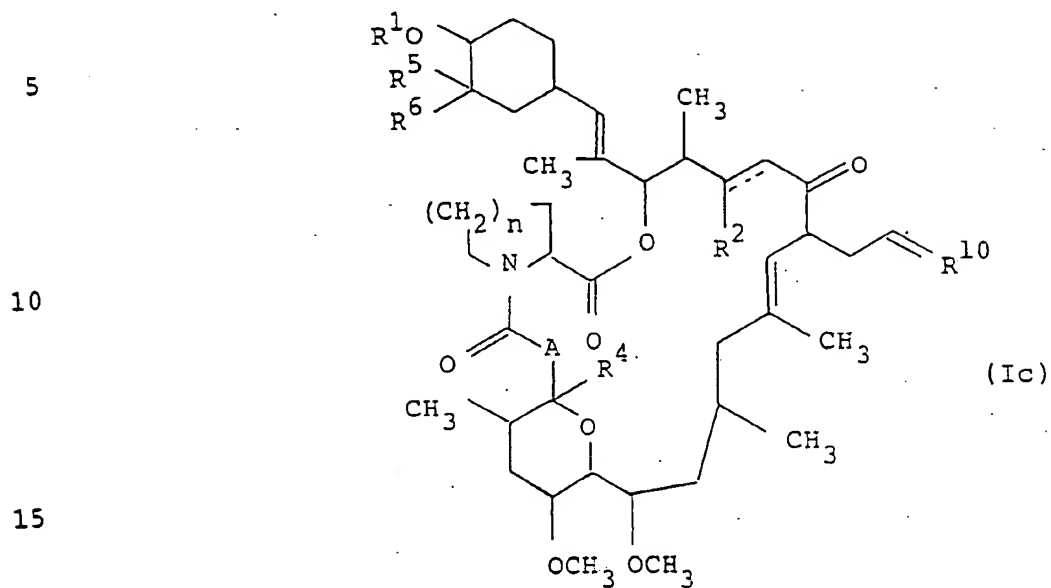
wherein R^7 is (C_2-C_6) alkyl, aryl (C_1-C_6) alkyl or
protected carboxy (C_1-C_6) alkyl,

R^8 is aryl,

R^9 is protected carboxy, and

35 X is halogen,

to give a compound of the formula :

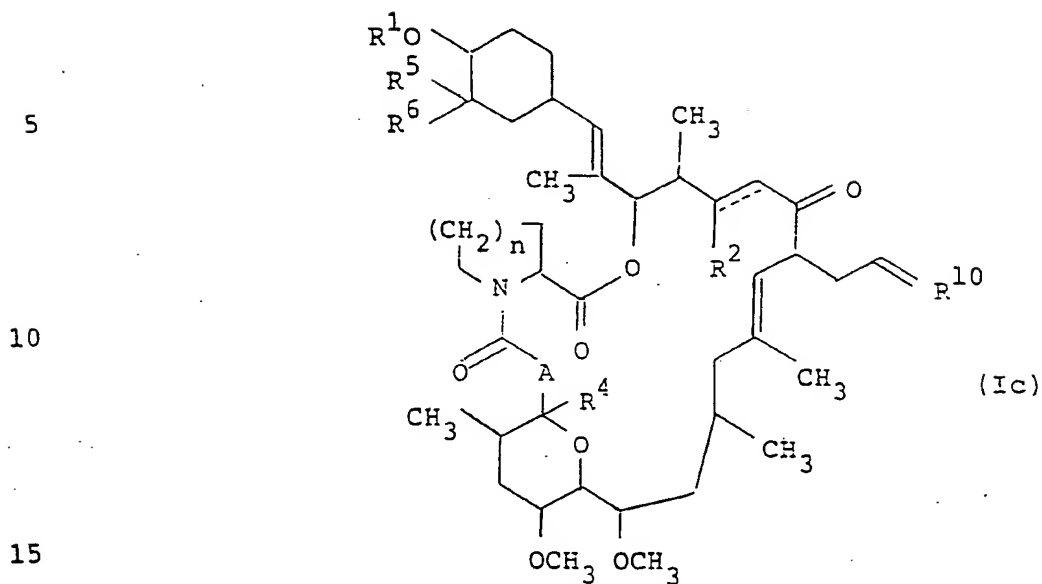


20 wherein R^1 , R^2 , R^4 , R^5 , R^6 , A, n and the symbol of a
line and dotted line are each as
defined above, and
 R^{10} is (C_2-C_6) alkylidene, aryl(C_1-C_6)-
alkylidene or protected
25 carboxy(C_1-C_6)alkylidene,
or a salt thereof; or

30

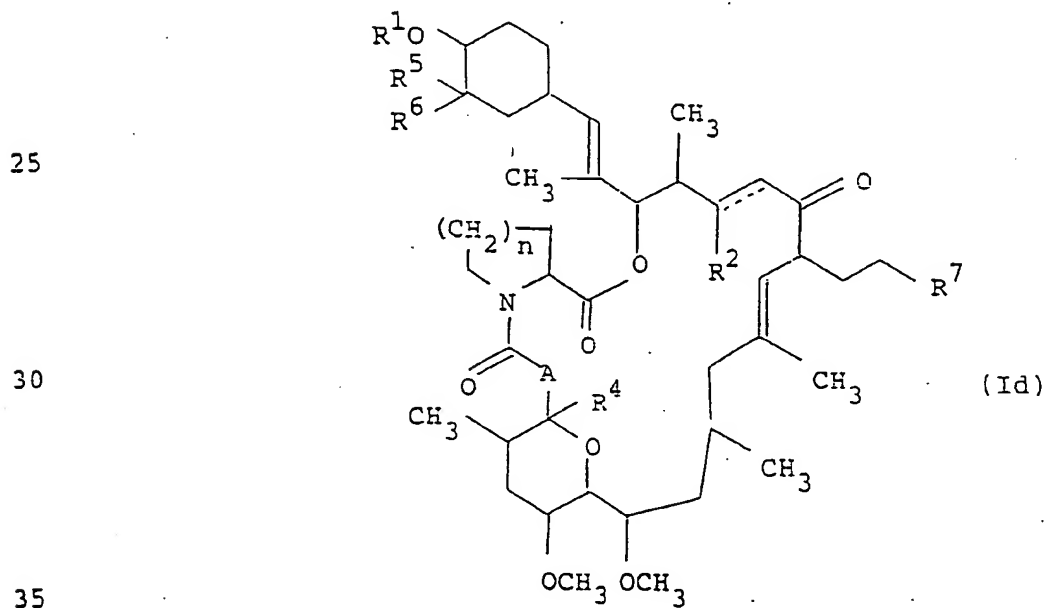
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(b) reducing a compound of the formula :



wherein R^1 , R^2 , R^4 , R^5 , R^6 , R^{10} , A, n and the symbol
of a line and dotted line are each as
defined above,

or a salt thereof, to give a compound of the formula:



wherein R^1 , R^2 , R^4 , R^5 , R^6 , R^7 , A, n and the symbol
of a line and dotted line are each as
defined above,
or a salt thereof.

- 5
3. A pharmaceutical composition containing tricyclo
compounds of claim 1, as an active ingredient, in
association with a pharmaceutically acceptable,
substantially non-toxic carrier or excipient.
- 10
4. A use of tricyclo compounds of claim 1 as a
medicament.
- 15
5. A method for treating or preventing resistance by
transplantation, graft-versus-host diseases by
medulla ossium, autoimmune diseases and infectious
diseases which comprises administering a compound of
claim 1 to human or animal.
- 20
6. A tricyclo compounds of Claim 1 for use as a
medicament.
- 25
7. A use of a tricyclo compound of Claim 1 for
manufacturing a medicament for treating or preventing
resistance by transplantation, graft-versus-host
diseases by medulla ossium, autoimmune diseases and
infectious diseases.
- 30
8. A process for preparing a pharmaceutical composition
which comprises admixing a tricyclo compound of Claim
1 with a pharmaceutically acceptable carrier or
excipient.
- 35

INTERNATIONAL SEARCH REPORT

International Application No

PCT/JP 91/00811

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC Int.Cl.5 C 07 H 19/01 A 61 K 31/70		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
Int.Cl.5	C 07 H 19/00 A 61 K 31/00	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹		
Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
A	EP-A-0 184 162 (FUJISAWA PHARMACEUTICAL CO., LTD) 11 June 1986, see pages 100-110 (cited in the application) ---	1-4, 6-8
A	EP-A-0 323 042 (FISONS PLC) 5 July 1989, see pages 18-21, (cited in the application) -----	1-4, 6-8
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>¹⁰ Special categories of cited documents : ¹⁰</p> <p>^{"A"} document defining the general state of the art which is not considered to be of particular relevance</p> <p>^{"E"} earlier document but published on or after the international filing date</p> <p>^{"L"} document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>^{"O"} document referring to an oral disclosure, use, exhibition or other means</p> <p>^{"P"} document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>^{"T"} later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>^{"X"} document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>^{"Y"} document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>^{"&"} document member of the same patent family</p> </div> </div>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search		Date of Mailing of this International Search Report
16-08-1991		19. 09. 91
International Searching Authority		Signature of Authorized Officer
EUROPEAN PATENT OFFICE		<div style="border: 1px solid black; display: inline-block; padding: 2px 10px;">M. PEIS</div> M. Pez

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☒ OBSERVATION WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE ¹

This International search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons

1. ☒ Claim numbers 5 because they relate to subject matter not required to be searched by this Authority, namely:
Pls. see Rule 39.1(iv) - PCT:
Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.
2. ☐ Claim numbers because they relate to parts of the International application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically
3. ☐ Claim numbers because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a)

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING ²

This International Searching Authority found multiple inventions in this International application as follows

1. ☐ As all required additional search fees were timely paid by the applicant, this International search report covers all searchable claims of the International application
2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the International application for which fees were paid, specifically claims:
3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims: It is covered by claim numbers
4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

- ☐ The additional search fees were accompanied by applicant's protest
- ☐ No protest accompanied the payment of additional search fees

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.**

JP 9100811
SA 48280

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 13/09/91. The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A- 0184162	11-06-86	AU-B- 592067	04-01-90
		AU-A- 5059685	12-06-86
		JP-A- 3072483	27-03-91
		JP-A- 3072484	27-03-91
		JP-A- 61148181	05-07-86
		US-A- 4956352	11-09-90
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		EP-A- 0346427	20-12-89
		WO-A- 8905304	15-06-89
		JP-T- 2502463	09-08-90